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Endocrinology Update

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Pheochromocytoma: Tips on Diagnosis and Localization

Catecholamine-secreting tumors that arise from chromaffin cells of the adrenal medulla and the sympathetic ganglia are referred to as *pheochromocytomas* and *extra-adrenal catecholamine-secreting paragangliomas (extra-adrenal pheochromocytomas)*, respectively. Because the tumors have similar clinical presentations and are treated with similar approaches, many clinicians use the term *pheochromocytoma* to refer to both adrenal pheochromocytomas and extra-adrenal catecholamine-secreting paragangliomas. However, the distinction between pheochromocytoma and paraganglioma is an important one because of implications for associated neoplasms, risk of malignancy, and genetic testing.

Catecholamine-secreting tumors are rare, with an annual incidence of 2 to 8 cases per 1 million people in all populations studied. William F. Young Jr, MD, of the Division of Endocrinology, Diabetes, Metabolism, and Nutrition at Mayo Clinic in Rochester, Minnesota, says: "Nevertheless, it is important to suspect, confirm, localize, and resect these tumors because 1) the associated hypertension is curable with surgical removal of the tumor, 2) a risk of lethal paroxysm exists, 3) at least 10% of the tumors are malignant, and 4) 10% to 20% are familial and detection of this tumor in the proband may result in early diagnosis in other family members."

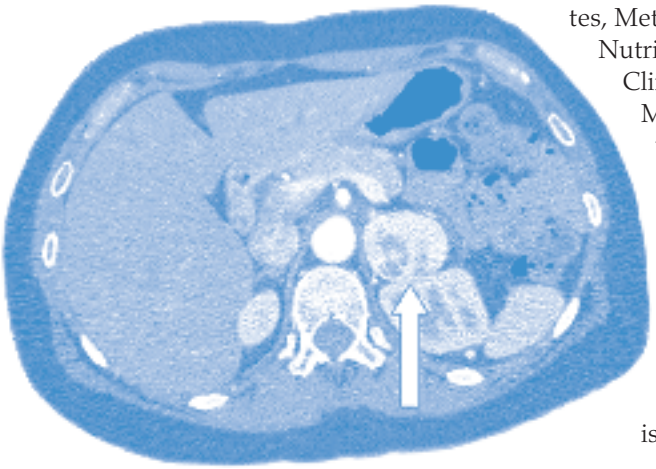


Figure. *Axial computed tomographic image of an asymptomatic patient with an incidentally discovered 5-cm left adrenal pheochromocytoma (arrow). This mass has an imaging phenotype consistent with pheochromocytoma: it is dense, vascular, and inhomogeneous. The Hounsfield unit density before contrast medium administration was 45. Ten minutes after administration, there was only 38% contrast washout.*

In 2009, pheochromocytoma is frequently diagnosed before symptoms develop because of genetic screening for hereditary endocrine syndromes or incidental discovery of adrenal mass on computed tomography (CT) or magnetic resonance imaging (MRI). Clive S. Grant, MD, of the Department of Surgery at Mayo Clinic in Rochester, says: "In many patients, catecholamine-synthesizing neoplasms are detected months or years before the onset of periodic hypersecretory states. Approximately 5% of all adrenal incidentalomas have proved to be pheochromocytomas. In the past, it was said that more than 95% of patients with pheochromocytoma had paroxysmal symptoms (spells) of palpitations, diaphoresis, and headaches. However, with the widespread use of CT and MRI, approximately 50% of all pheochromocytomas are initially detected as adrenal incidentalomas in patients without spells and, frequently, without hypertension."

Dr Grant continues: "It is important to recognize that in a patient with spells, the degree of increase in fractionated metanephrines and catecholamines in the blood or urine should be markedly abnormal. In other words, if a pheochromocytoma is responsible for 'classic pheochromocytoma spells,' then the biochemical test results are always unequivocally

abnormal (eg, increases more than 5 times the upper limit of the reference range). However, in the asymptomatic patient with pheochromocytoma, fractionated metanephrines and catecholamines may be normal because the neoplasm has been detected in the 'prebiochemical phase.' In this situation, the clinician must rely on the features of the mass on CT or MRI (the imaging phenotype) to guide management. Thus, the imaging phenotype of an adrenal mass can be more important than biochemical testing."

Plasma fractionated metanephrines have a 15% false-positive rate (usually because of increased plasma normetanephrine concentrations). Dr Young explains: "Because of this high false-positive rate and the rarity of pheochromocytoma, at Mayo Clinic 97% of patients with plasma normetanephrine concentrations above the upper limit of the reference range do not have a pheochromocytoma. Another caution on biochemical testing relates to the reference range for 24-hour urinary fractionated metanephrines. Most reference laboratories have standardized their 24-hour fractionated metanephrine assays on the basis of healthy laboratory volunteers who are drug free and have normal blood pressure. I have never tested such a person for pheochromocytoma."

Box 1 shows the upper limits of the reference ranges based on patients who are investigated for pheochromocytoma but prove to not have this rare tumor. Patients with values above these diagnostic cutoffs either have pheochromocytoma, are severely ill (eg, hospitalized in an intensive care unit), or are taking a medication that is causing false-positive test results (Box 2). Dr Young says: "It is important to note that use of antihypertensive agents (eg, β-adrenergic blockers, α-adrenergic inhibitors) and selective serotonin reuptake inhibitors does not result in false-positive biochemical test results."

Box 1. Upper Limit of Reference Ranges for 24-Hour Urinary Fractionated Metanephrines and Catecholamines

- Metanephrine <400 mcg
- Normetanephrine <900 mcg
- Total metanephrine <1,000 mcg
- Norepinephrine <170 mcg
- Epinephrine <35 mcg
- Dopamine <700 mcg

Box 2. Medications and Situations That Can Cause False-Positive Results on Biochemical Testing for Pheochromocytoma

- Tricyclic antidepressants (including cyclobenzaprine hydrochloride)
- Levodopa
- Ethanol withdrawal
- Withdrawal from clonidine and other drugs (eg, illicit drugs)
- Antipsychotics, buspirone hydrochloride, and bupropion hydrochloride
- Amphetamines
- Prochlorperazine
- Reserpine
- Major physical stress (eg, surgery, stroke)
- Obstructive sleep apnea syndrome

After biochemical confirmation of pheochromocytoma, CT or MRI of the abdomen and pelvis is the first localization test. Dr Grant notes: "Approximately 90% of these tumors are found in the adrenals and 98% in the abdomen and pelvis. If the abdominal imaging result is negative, then scintigraphic localization with ^{123}I-metaiodobenzylguanidine (^{123}I-MIBG) is indicated. Computer-assisted chest, neck, and head imaging provides additional localizing procedures that can be used, though they are rarely required. The tumor can always be found in symptomatic patients with pheochromocytoma, because the average diameter of a pheochromocytoma in this situation is 4.5 cm. The typical imaging phenotype of a pheochromocytoma is a dense (Hounsfield units, >20) and vascular mass with slow contrast washout (<50% at 10 minutes after contrast medium administration) (Figure 1, see page 1). By comparison, the much more common adrenocortical adenoma is usually hypodense (Hounsfield units, <10) and has rapid contrast washout (>50% at 10 minutes) (Figure 2). When the clinician is having trouble localizing a pheochromocytoma, it is usually because the patient does not have pheochromocytoma. Medication-induced false-positive biochemical test results and use of inappropriately

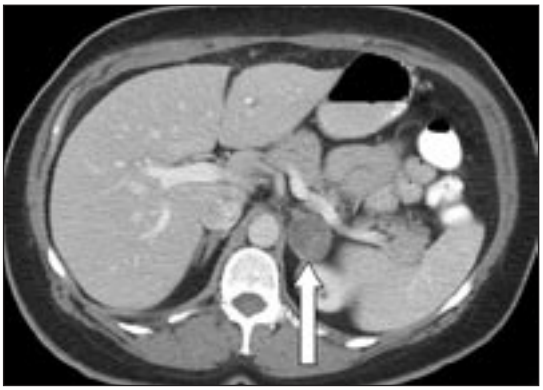


Figure 2. *Axial computed tomographic image of an asymptomatic patient with an incidentally discovered 2.5-cm left adrenal mass (arrow). This mass has an imaging phenotype consistent with a cortical adenoma: it is hypodense, not vascular, and homogeneous. The Hounsfield unit density before contrast medium administration was –5. Ten minutes after administration, there was 70% contrast washout.*

Clive S. Grant, MD, and William F. Young Jr, MD

low reference ranges can lead to imaging misadventures. Finally, it is important for the clinician to understand that ^{123}I-MIBG is taken up by healthy adrenal glands and the intensity of uptake is usually asymmetrical. An adrenal gland should never be resected on the basis of asymmetrical adrenal uptake of ^{123}I-MIBG unless the uptake pattern correlates with a vascular adrenal mass on CT."

Case Detection of Cushing Syndrome in Adults

Endogenous Cushing syndrome (CS) is a rare condition with an incidence of 1 to 2.5 cases per 1 million persons per year in the United States. CS is associated with increased morbidity and death. The typical clinical features of hypercortisolism include central weight gain, easy bruising, facial plethora and rounding of the face (moon facies), emotional lability, insomnia, proximal muscle weakness, supraclavicular fullness, dorsocervical fat pad, amenorrhea, hypertension, hyperglycemia, osteopenia or osteoporosis, and wide purple-red striae over the abdomen, inner thighs, and axilla. Dana Erickson, MD, of the Division of Endocrinology, Diabetes, Metabolism, and Nutrition at Mayo Clinic in Rochester, Minnesota, notes, "When patients present with signs and symptoms consistent with CS, the clinician should first exclude exogenous corticosteroid use and then pursue biochemical testing. We frequently encounter patients with mild signs and symptoms that may be consistent with CS—a presentation that overlaps with frequent problems seen in the general population, such as obesity, metabolic syndrome, depression, and menstrual irregularities. Therefore, it is important for us to have a good understanding of the diagnostic accuracy of the currently available tests for evaluation of hypercortisolism."

The 3 standard case detection tests for CS are 24-hour urinary free cortisol (UFC); late-night salivary cortisol; and 1-mg overnight dexamethasone suppression test (DST). UFC measures cortisol that is not bound to cortisol-binding globulin and represents integrated adrenal cortisol secretion over 24 hours. Ravinder J. Singh, PhD, of the Department of Laboratory Medicine and Pathology at Mayo Clinic in Rochester, explains: "Our laboratories use liquid chromatography–tandem mass spectrometry (LC-MC/MS) for measurements of cortisol. To ensure accuracy, we confirm that the patient 1) has completed an entire 24-hour urine collection (typically assessed with measurement of urinary creatinine), 2) does not have excessive fluid intake (24-hour urine volumes more than 5 L can result in falsely elevated levels of cortisol excretion), and 3) has normal renal function (renal failure can decrease urinary cortisol excretion)."

Dr Erickson highlights: "It is important to note that one out of four 24-hour UFC measurements in the setting of true CS can be within normal limits. Thus, when the UFC result is normal but the clinical suspicion for CS is high,

the 24-hour UFC measurements should be repeated several times (eg, weekly or monthly). CS is confirmed when the 24-hour UFC is more than 3-fold increased above the upper limit of the reference range. The test characteristics of 24-hour UFC include sensitivities of 76% to 100% and specificities of 95% to 98%. (The variation depends on patient population, reference range, and type of assays used.) The interpretation of urinary cortisol excretion should incorporate the degree of clinical suspicion for CS."

Late-night salivary cortisol, collected at 11:00 PM with a salivate-collecting device (Figure), is an attractive option for CS case detection because it assesses cortisol secretion at the physiologic nadir. Dr Singh explains: "At Mayo Medical Laboratories, we use LC-MC/MS to measure salivary cortisol. When the sample is obtained at 11:00 PM, the upper limit of the reference range is 100 ng/dL. Based on published studies, the salivary cortisol test characteristics include a sensitivity of 93% to 100% and a specificity of 85% to 100%. However, our preliminary data suggest that the true sensitivity may be lower than previously reported."

Another useful detection test is the 1-mg overnight DST, in which dexamethasone is administered between 11:00 PM and midnight and the serum cortisol concentration is measured between 8:00 and 9:00 AM the following morning. Normal suppression is defined as a serum cortisol concentration less than 1.8 mcg/dL (sensitivity, 95%; specificity, 80%). Dr Erickson explains: "If the diagnostic threshold is raised to 5 mcg/dL, the specificity increases to 95% but sensitivity declines. Interpretation of DST results can be confounded by medications that accelerate the metabolism of dexamethasone (eg, anticonvulsants) or medications that increase serum cortisol-binding globulin concentrations (eg, oral estrogens)."

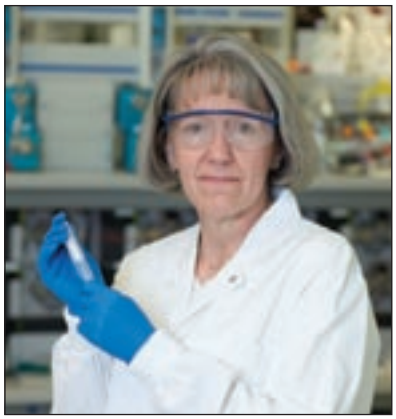


Figure. *Mary L. Eastvold, assistant supervisor, of the Mayo Clinic Endocrine Laboratory, holding a salivette that is used for collection of saliva for cortisol testing.*

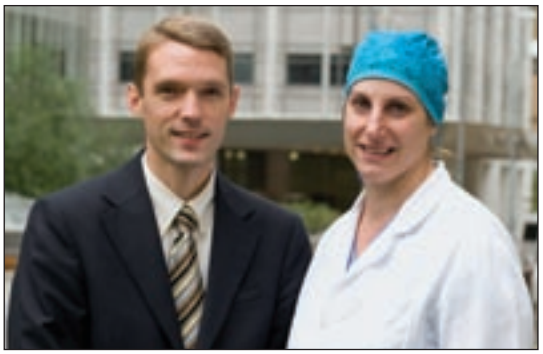
Dana Erickson, MD, and Ravinder J. Singh, PhD

What should the clinician do when the findings of the 24-hour UFC, late-night salivary cortisol, and 1-mg overnight DST are equivocal or inconclusive? Dr Erickson answers: "When the findings from the 3 standard case detection tests are inconclusive, there are 2 options to consider. One option is to reassess 3 to 6 months later. If a patient has true CS, the signs and symptoms and the levels of cortisol secretory abnormalities should progress over time. Another option is to perform a combined corticotropin-releasing hormone–DST (CRH-DST). The basis for the CRH-DST is that tumorous corticotroph cells respond to CRH in the presence of dexamethasone, whereas normal corticotroph cells do not respond. Our experience with 51 patients (21 with CS and 30 without CS) showed that a 15-minute post-CRH serum cortisol concentration greater than 2.5 mcg/dL resulted in sensitivity and specificity of 90% each. In addition, a serum corticotropin concentration greater than 27 pg/mL at 15 minutes after CRH administration provided a sensitivity of 95% and a specificity of 97% for diagnosis of CS."

Dr Erickson concludes: "We recommend that, to establish a diagnosis of CS, at least 2 case detection tests should have abnormal results. However, sound clinical judgment should guide the interpretation of laboratory tests, and in many instances, close follow-up of the patient and repeat testing are necessary to establish a firm diagnosis of CS before initiating further evaluation and treatment."

Childhood Fractures: When to Worry

Childhood bone fractures are common and often cause concern for patients, parents, and clinicians. This concern is especially true when a child has had more than 1 fracture. Peter J. Tebben, MD, of the Division of Endocrinology, Diabetes, Metabolism, and Nutrition and the Division of Endocrinology in the Department of Pediatrics at Mayo Clinic in Rochester, Minnesota, outlines: "Approximately one-third of children will have sustained a fracture [Figure 1A] by age 18 years. Most of these children do not have an underlying metabolic bone disorder that requires evaluation and treatment. It is often hard to know when to worry about fractures in children and decide who needs further evaluation for potential underlying disease. Understanding the typical timing and types of fractures is helpful. The rate of fractures increases substantially during puberty for both boys and girls but to a greater degree for boys. The peak incidence of fractures in girls occurs around 10 to 12 years of age and in boys around 13 to 15 years of age. Forearm fractures are by far the most common type of fracture during childhood. However, vertebral compression fractures are distinctly uncommon in children [Figure 2] and should always be a cause for concern and additional evaluation."



Peter J. Tebben, MD, and Amy L. McIntosh, MD

When to Worry

Children with 1 or 2 traumatic fractures are unlikely to have an identifiable disorder and do not routinely require further evaluation. Dr Tebben notes: "Obtaining a detailed history about the circumstances surrounding a fracture is important in determining the level of concern. Multiple fractures, atypical fractures (such as vertebral compression fractures), low-trauma fractures, and a family history of metabolic bone disease are all red flags that should prompt further investigation. Children with inflammatory bowel disease, celiac disease, chronic glucocorticoid exposure, neuromuscular disorders, and others [Box] warrant special attention to optimize bone health, since they are at increased risk for low bone density. A family history of frequent fractures should prompt consideration of inherited conditions, such as osteogenesis imperfecta."

Amy L. McIntosh, MD, of the Division of Pediatric Orthopedics in the Department of Orthopedic Surgery at Mayo Clinic in Rochester, says: "Unexplained fractures, especially in infants, mandate consideration of nonaccidental trauma if an underlying bone disorder is not clearly identified. Poor fracture healing also should raise suspicion of an underlying bone disease. Most fractures in children show radiographic evidence of callus formation by 3 to 6 weeks. By 8 to 12 weeks, most fractures are united radiographically [Figure 1B and 1C] and no longer require any form of external immobilization."

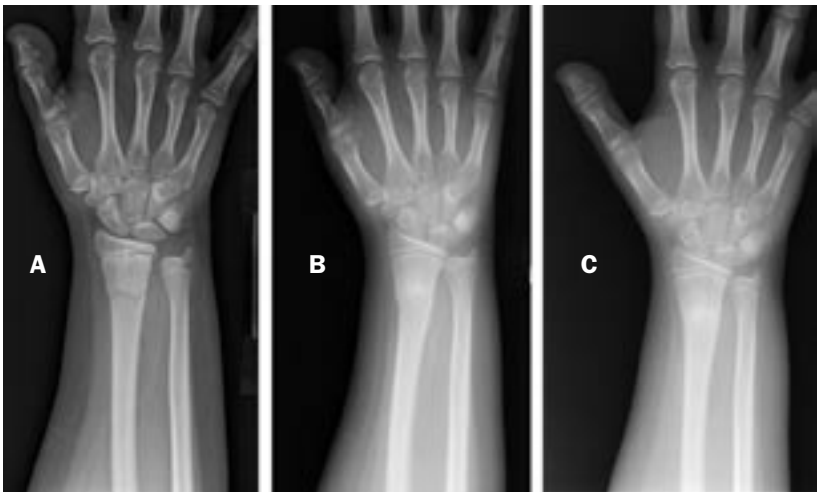


Figure 1. *Trauma-related fracture of the distal radius. A, Radius shortly after injury. B and C, Subsequent normal bone healing.*

Evaluation

A basic laboratory evaluation includes such tests as serum calcium, phosphorus, creatinine, parathyroid hormone, 25-hydroxyvitamin D, and urine calcium determination. Dr Tebben explains: "The serum concentration of 25-hydroxyvitamin D is the best test to determine whether

Box. Conditions Associated With Low Bone Density or Fractures in Children

- Anorexia nervosa
- Anticonvulsant use
- Dietary calcium deficiency
- Glucocorticoid excess
- Growth hormone deficiency
- Homocystinuria
- Hyperthyroidism
- Hyperparathyroidism
- Idiopathic juvenile osteoporosis
- Immobilization
- Leukemia
- Malabsorption (eg, celiac disease, inflammatory bowel disease)
- Neuromuscular disorders
- Osteogenesis imperfecta
- Osteoporosis pseudoglioma syndrome
- Vitamin D deficiency

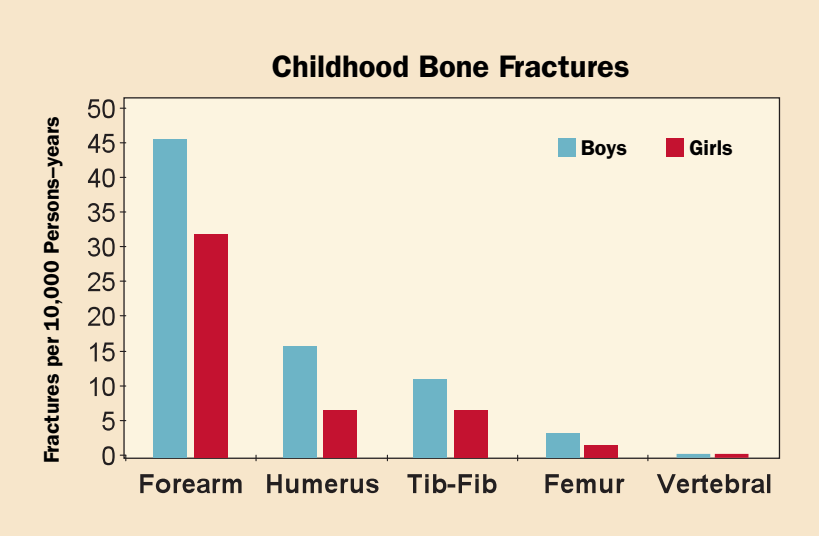


Figure 2. *Incidence of specific fracture types in children. Data from Cooper C, Dennison EM, Leufkens HGM, Bishop N, van Staa TP. Epidemiology of childhood fractures in Britain: a study using the general practice research database. J Bone Miner Res. 2004 Dec;19(12):1976-81. Tib-Fib indicates tibia and/or fibula.*

adequate vitamin D stores are present. The serum concentration of the active metabolite of vitamin D (1,25-dihydroxyvitamin D) can be variable in children with nutritional vitamin D deficiency (low concentration of 25-hydroxyvitamin D) and is usually not helpful in determining vitamin D status. Serum alkaline phosphatase values are helpful but can be difficult to interpret in children. Growing children have a markedly greater serum alkaline phosphatase concentration than adults, and an appropriate reference range for age and sex should be used. Alkaline phosphatase level will usually be elevated in the context of a recently sustained, healing fracture. Clinical findings supporting a secondary cause of poor bone health [Box] should also guide the evaluation."

Dual-energy x-ray absorptiometry (DXA) is a widely available technique for determining bone density. Children with frequent, low-trauma, or atypical fractures are good candidates for bone density measurement. Dr Tebben says: "Children with disorders associated with low bone density, such as inflammatory bowel disease, may also benefit from bone density determination. DXA measurements in children should be performed in centers with experience obtaining and interpreting the scan. An appropriate normative database is needed for interpretation of the result. The Z-score compares an individual's bone density to an age- and sex-matched normal population and is the appropriate measure to use when interpreting bone density in children. T-scores should never be used in children because they will lead to unnecessary concern and unneeded evaluation."

Prevention

Adequate intake of calcium and vitamin D is the foundation of any treatment program to promote bone health. The American Academy of Pediatrics currently recommends that all children receive 400 IU of vitamin D daily, which can be obtained through the diet (mainly milk) or through supplementation, or both. The optimal amount of vitamin D intake or serum vitamin D concentration for children has not yet been clearly defined. Avoiding excessive caffeine and soda intake should also be advised.

Dr Tebben notes: "Bisphosphonates may be beneficial in select children with low bone density and fractures and should be given under the supervision of a clinician experienced with their use in children. Bisphosphonates are not approved by the US Food and Drug Administration for use in children, and only minimal data exist regarding fracture prevention in children."

New Technologies in Diabetes Mellitus

Continuous subcutaneous insulin infusion (CSII), or insulin pump therapy, continues to improve incrementally in clinical practice since its introduction in 1979. Yogish C. Kudva, MBBS, of the Division of Endocrinology, Diabetes, Metabolism, and Nutrition at Mayo Clinic in Rochester, Minnesota, says: "Two technologies currently infuse insulin continuously into subcutaneous tissue. The first option is a conventional insulin pump that consists of a subcutaneous cannula connected through tubing to an insulin reservoir in a small (eg, 6 × 4 × 1.5 cm) pump clipped to the patient's apparel [Figure]. With the second option—termed CSII without conventional tubing—the cartridge with insulin is a pod that is secured to the skin with tape [Figure]. The cannula insertion is automated and part of the pod, thus avoiding

the need for cumbersome tubing from the insertion site to the CSII device."

Dr Kudva notes: "CSII programs continue to become more sophisticated, with each vendor seeking to offer unique options. These options include smart programming, ease of use in real time by the patient, and methods to converge devices and diabetes management software. Smart programming offers refinement and safety features in basal insulin delivery—including multiple basal patterns with designation of patterns for work days, week days, and vacation days. Smart programming involving insulin bolus administration provides the delivery of bolus over a defined period. Ease of use in real time by the patient includes initiatives directed toward the options available on the pump screen and the ability to calculate calories and carbohydrates ingested. Convergence of devices addresses the issue of merging the glucose reflectance meter data and the insulin delivery device through wireless communication between the two or merging of both devices into one."

Continuous Glucose Monitoring

Continuous glucose monitoring (CGM) with subcutaneous probes provides interstitial fluid glucose measurements every 5 minutes for a minimum of 3 days and a maximum of 7 days (Figure). Dr Kudva explains: "Glucose sensors may display glucose data in real time or merely record glucose data to be downloaded at the end of the life of the disposable sensor probe (diagnostic CGM). Real-time data are displayed usually on a sensor device or a pump. Real-time glucose sensors were used by patients with type 1 diabetes in a trial funded by the Juvenile Diabetes Research Foundation Clinical Trial. In this trial, the use of CGM for adult patients with glycosylated hemoglobin values greater than 7.5% resulted in improved glycemic control without an increased incidence of hypoglycemia. Clinical use of a CGM requires a close partnership between the patient and an expert team. Use of a CGM also involves issues such as data overload and the disruptive frequency of alarms for low and high blood glucose concentrations."

Pathway to an Artificial Pancreas

Advances in CGM and CSII have hastened the development of an artificial endocrine pancreas, a technology that the US Food and Drug Administration (FDA) has designated as a critical pathway. An in silico artificial pancreas has been developed by a multicenter team and has been approved by the FDA. Dr Kudva says: "Studies on the artificial pancreas are currently underway using this model predictive control algorithm. In addition, the National Institutes of Health has recently awarded grants with the intent to hasten the pace of closed-loop studies. Our multidisciplinary group has been awarded a grant through this program, to start December 1, 2009."

Implications for Diabetes Care

Dr Kudva concludes: "Specialist clinics need additional information technology infrastructure to analyze blood glucose and insulin administration data to guide treatment. Software development is needed so that uniform analysis can be performed on data from devices that are manufactured by several vendors. When developed, such software would enable medical care to be provided from a distance—a worthwhile endeavor in a globalized world."

Figure. *Yogish C. Kudva, MBBS, with various insulin pumps and continuous glucose monitors.*

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CME Opportunities

13th Mayo Clinic Endocrine Course

July 14-17, 2010, Rochester, Minnesota. This course, created for endocrinologists and interested internists and surgeons, will present the latest material on the diagnosis and treatment of endocrine disorders. For more information about this course, please call 800-323-2688 or visit www.mayo.edu/cme/endocrinology.html.

Award Announcement

Mayo Brothers Inducted Into Health Care Hall of Fame

William J. "Will" Mayo, MD, and Charles H. "Charlie" Mayo, MD, founders of Mayo Clinic, were inducted into the Health Care Hall of Fame on March 22, 2009, in conjunction with the American College of Healthcare Executives' 2009 Congress on Healthcare Leadership. The annual honors program is sponsored by *Modern Healthcare* magazine, and inductees are determined by a panel of judges selected from the industry. "The Mayo brothers pioneered the group practice of medicine—an innovative way to organize and deliver care to patients. Today, we are determined to build upon their legacy by bringing patient-centered health care reform to this country," says Denis Cortese, MD, president and CEO of Mayo Clinic.

Perspective on the Mayo brothers' pioneering work in health care was provided by Donald M. Berwick, MD, president and CEO of the Institute for Healthcare Improvement and a leading national authority on health care quality and improvement issues. According to Dr Berwick, "Drs Will and Charlie combined visionary ideals with practical skills. That same integrated approach, which puts the needs of the patient first, is still in place at the Mayo Clinic today. As we look at national health care reform efforts, the Mayo model of care also provides a real-life example of the best forms of teamwork to deliver high-value care."

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